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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/839,658

Filing Date: April 19, 2001
Appellant(s): BRADLEY ET AL.

Christopher R. Rhodes
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 18, 2007 appealing from the Office action mailed December 13, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

A substantially correct copy of appealed claims 1-14, 17, 67, 68 and 72 appears on page 16-20 of the Appendix to the appellant's brief. The minor errors are as follows: in claim 1, line 7, the phrase "each probe is a vector" was amended on November 13, 2006 to "each probe in a vector", however, claim 1 as presented in the appendix contains the phrase "each probe is a vector", even though the amendment was entered.

(8) Evidence Relied Upon

GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Interpretation

1. Applicants did not define the term "about X bases", therefore, for example, the term "about 30 bases" is interpreted as any number of bases between one and 100, for example. In addition, the phrase "greater than about X bases" is interpreted as any number of bases, as are phrases "smaller than about X bases" and "no more than about X bases".

2. With respect to the term "stringent hybridization conditions", Applicants provided the following description (page 13, lines 14-19 and 29-31; page 14, line 1):

> "...The term "stringent conditions" refers to conditions under which a probe will hybridize preferentially to its target subsequence, and to a lesser extent to, or not at all to, other sequences. A "stringent hybridization" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization (e.g., as in array, Southern or Northern hybridizations) are sequence dependent, and are different under different environmental parameters." And
>
> "...However, the selection of a hybridization format is not critical, as is known in the art, it is the stringency of the wash conditions that set forth the conditions which determine whether a nucleic acid is within the scope of the invention."

Therefore, depending on the length of the nucleic acids participating in the hybridization reaction, different conditions will be considered as being "stringent".

3. Note: the rejections presented here addressed claims before their amendment after final on November 13, 2006, hence the claim interpretation includes the interpretation of the term "about", which is no longer present in the claims.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-6, 12-14, 17, 67, 68 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993).

A) Regarding claim 1, Kallioniemi et al. teach detection gene copy number amplifications or deletions by hybridization of target nucleic acids to an array of plurality of immobilized probes by the method comprising:

(a) providing the plurality of nucleic acid probes comprising a plurality of immobilized nucleic acid segments in an array with each probe at a known location, wherein each probe is a member of a genomic library cloned in a vector, and each probe is the vector having a cloned nucleic acid insert greater than 50 kilobases, wherein the plurality of probes represents all of the chromosome or a genome (Kallioniemi et al. teach CGH (comparative genomic hybridization) arrays (page 2, [0013], [0022]), and DNA arrays in which large-insert genomic clones such as P1, BAC or PAC clones are attached to solid support (page 3, 4 [0053]). Kallioniemi et al. teach an array of clones representing all of the human genome (page 14, [0152], [0153]). Kallioniemi et al. teach an array of P1, BAC or PAC clones each of which has an insert of 80 to 150

kilobases (page 15, [0156]). Kallioniemi et al. teach an array of clones at known locations (Fig. 14).);

(b) contacting the immobilized probes with a sample of target nucleic acid comprising fragments of genomic nucleic acid, wherein said fragments include both strands of a double-stranded genomic DNA fragment and include at least 30% repetitive sequences, and wherein both strands are labeled with a detectable moiety, wherein each labeled fragment consists of a length smaller than 200 bases, and the contacting is under conditions allowing specific hybridization of both strands of the labeled fragment of the target nucleic acid to the probe nucleic acid (Kallioniemi et al. teach contacting genomic DNA target labeled with a fluorescent dye (= detectable moiety) to a CGH array (page 14, [0152]). The target DNA is contacted with the immobilized probes under conditions which permitted specific hybridization of the target to the probes (page 2, [0016]). Kallioniemi et al. teach human genome (page 14, [0153]). Therefore, since human genome contains at least 30% of repetitive sequences, by teaching human genome Kallioniemi et al. inherently anticipate this limitation.); and

(c) observing an amount and location of labeled genomic nucleic acid hybridized to each immobilized probe, to detect regions of amplification or deletion in the sample, wherein positional information of clones on the arrays and chromosomes is correlated, thereby generating a molecular profile of the chromosome or genome of the sample genomic nucleic acid (Kallioniemi et al. teach observation of hybridization events using a CCD camera and detection gene amplifications or deletions on chromosomes (page 2, [0013], [0016]; page 15 [0157], [0160]).).

Regarding claims 12 and 13, Kallioniemi et al. teach hybridization conditions of 42° C and wash of 55° C (page 8, 9, [0100], therefore, according to Applicants' description, they teach stringent hybridization conditions and temperature about 60° C.

Regarding claim 14, Kallioniemi et al. teach target nucleic acid consisting of human DNA (page 14, [0152]).

Regarding claim 17, Kallioniemi et al. teach human genome (page 14, [0153]).

Regarding claims 67 and 72, Kallioniemi et al. teach the sample nucleic acid being chromosome 22 (page 10, [0116]).

Regarding claims 68 and 72, Kallioniemi et al. teach the sample nucleic acid being total human DNA, therefore anticipating the limitations of a sample comprising at least one chromosome and a sample comprising a complete genome (page 14, [0152]; page 15, [0156]).

B) Kallioniemi et al. do not teach DNA fragments with length of less than 200 bp to less than 30 bp.

C) Regarding claims 1-6, 70 and 71, McGill et al. teach detection of chromosome 8 amplification using probes derived from the chromosome (col. 3, lines 56-67; col. 4, lines 16). The probe lengths were 10-500 bp (col. 5, lines 35-45 and 52-55), with the optimal probe sequence being about 20 bases (col. 6, lines 1-10). Therefore, since the probes of McGill et al. are shorter than 200 bp, the result of using them in hybridization would be less probe aggregation and lower hybridization background, since each of the probes would anneal to a 20 bp sequence which appears once in 4^{20} bp in the genome, or once every 1,099,511,627,776 bp in the genome (as compared to human genome size of 3,000,000,000 bp), that binding of such probes will be very specific, therefore reducing background and non-specific aggregation.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used short probes of McGill et al. in the hybridization method of Kallioniemi et al. The motivation to do so, provided by McGill et al., would have been that probes with about 20 bases allows formation of duplexes which are stable and selective (col. 6, lines 1-3).

Additional motivation for using short probes is provided by Pollack et al., who teach hybridization of DpnII digested and labeled genomic DNAs to cDNA arrays (Abstract; page 46, first paragraph). They found that reducing the size of genomic DNA before labeling improved labeling efficiency by providing greater accessibility of the DNA template following digestion. Such greater accessibility would also allow more specific annealing of the probes to the array.

D) Neither Kallioniemi et al. nor McGill et al. specifically teach double-stranded DNA fragments labeled on both strands.

E) Pollack et al. teach labeling of genomic DNA digested with DpnII and labeling the genomic DNA with a BioPrime labeling kit from GibcoBRL (page 46, first paragraph) for hybridization to a cDNA array. As evidenced by the GibcoBRL catalog, the BioPrime labeling kit contains a DNA polymerase and random primers (page 18-16), therefore, the labeling reaction would result in amplified double-stranded DNA with both strands labeled.

It would have been *prima facie* obvious to have used the BioPrime labeling kit of GibcoBRL to produce double-stranded labeled DNA fragments in the method of Kallioniemi et al., McGill et al. and Pollack et al. The motivation to do so is provided by Mackey et al., who teach using the BioPrime kit to label genomic DNA to create probes for hybridization, and teach that probes were prepared from as little as 1 ng of starting material (Abstract), and, as stated by Mackey et al. (page 434, last paragraph):

"In summary, the random primer biotin labeling system described here has a number of attractive features. Small amounts of template DNA (as little as 1 ng) can be amplified and labeled resulting in hundreds of nanograms to microgram of biotinylated probe. This amplification method is especially useful for labeling of DNAs which are difficult to isolate in large quantities; these include YACs, cosmids and DNA isolated from agarose and polyacrylamide gels. The probe size is small and and is suitable for in situ hybridization procedures."

6. Claims 7, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action) and Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993), as applied to claim 1 above, and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action).

A) Regarding claim 7, Kallioniemi et al. teach generation of nucleic acids by polymerase chain reaction, nick translation or random priming (page 10, [0114]-[0116].

Regarding claim 8, Kallioniemi et al. teach labeling of nucleic acid fragments by nick translation or random priming (page 10, [0116]).

B) Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. do not teach fractionation of DNA by DNAse digestion.

C) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used DNAse I digestion of Anderson to fragment genomic target DNA in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Anderson, would have been that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (page 3019, first two paragraphs).

7. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action), as applied to claim 8 above, and further in view of Waggoner et al. (U. S. Patent No. 5,268,486; cited in the previous office action).

A) Claim 9 is drawn to the label comprising Cy3 or Cy5.

B) Kallioniemi et al. and McGill et al. teach fluorescent labels, but do not teach Cy3 or Cy5.

C) Waggoner et al. teach luminescent cyanine dyes, including Cy3 and Cy 5 (col. 19, formula at the bottom; claim 8; Cy3 has m=1, Cy5 has m=2). The dyes are be used to label nucleic acids (col. 2, lines 58-61; col. 4, lines 29-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the cyanine dyes of Waggoner et al. in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by

Waggoner et al., would have been that cyanine dyes were used for detecting mixtures of components because they had a wide range of excitation and emission wavelengths (col. 4, lines 36-49).

8. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action), as applied to claim 1 above, and further in view of Ordahl et al. (Nucl. Acids Res., vol. 3, pp. 2985-2999, 1976; cited in the previous office action) and Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action).

A) Claim 11 is drawn to fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

B) Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. do not teach fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

C) Ordahl et al. teach fragmentation of genomic DNA in preparation for DNA hybridization experiments. Ordahl et al. teach that it is advantageous to use DNA fragments of less than 500 bp in hybridization experiments (page 2985, first paragraph). Ordahl et al. teach that DNA fragmented in French press had an average size of 230 base pairs (Abstract; page 2986; Fig. 4). Ordahl et al. do not teach DNAse I fragmentation after shearing.

D) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used shearing of Ordahl et al. and DNAse I digestion of Anderson to fragment genomic target DNA in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Ordahl et al. and Anderson, would have been that it was advantageous to use short DNA fragments in hybridization (Ordahl, p. 2885, first paragraph) and that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (Anderson, page 3019, first two paragraphs).

(10) Response to Argument

Appellant presented the following issues regarding the rejections:

I. Scope of the term "about".

Appellant argues that even though the term "about" has not been defined, "the meaning and scope of such terms are intended to be flexible and can vary based on the context of their usage". Appellant further argues that a description in paragraph [0006] indicates that the number of bases in nucleic acid fragments has a lower limit of about 25 bases and an upper limit of about 200 bases, therefore the interpretation of the term "about" as meaning any number of bases is incorrect.

What Appellant is arguing is that the meaning of the word "about" is defined by phrases which contain the word "about". However, regardless of the interpretation, the prior art used, McGill et al., teaches fragments of 10-500 bp, which anticipate the range of sizes of "about 25 to

about 200 base pairs". Finally, this term is not used in the currently pending claims with respect to nucleic acid fragment length.

II. Rejection of claims 1-6, 12-14, 17, 67, 68 and 72 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al.

Appellant argues the following:

A) Kallioniemi does not disclose, teach or suggest a method that uses, in part, a plurality of immobilized nucleic acid probes that are a collection of clones that represent all of a chromosome or a genome of an organism, and contacting such probes with labeled, double-stranded genomic DNA fragments." Appellant continues: "In contrast to Appellant's claims, Kallioniemi describes a genosensor that scans the human genome for large deletions or duplications in a single assay (emphasis added, page 14 Par. No. [0152], [0153])." Appellant follows with "Scanning human genome using a genosensor in a single assay, as disclosed in Kallioniemi, is not the same method that uses a plurality of immobilized nucleic acid segments in an array that are a collection of clones that represent all of a chromosome or a genome of an organism as defined by claim 1. Many arrays can be used in a single assay to scan the human genome using a genosensor as disclosed in Kallioniemi, whereas a single array of claim 1 may comprise a collection of clones that represent all of a chromosome or a genome of an organism." (page 9 of the Brief, second paragraph).

First, Appellant's argument compares apples and oranges, i.e., the structure of Appellant's claimed array with the function of Kallioniemi's array, without mentioning the structure of it. So, let us analyze Kallioniemi's teachings. As recited in the previous office action, Kallioniemi et al. specifically teach an array of nucleic acid probes (= genosensor) cloned

into vectors (page 3, 4 [0053]; page 14, [0152], [0153]), with the vectors being P1, BAC or PAC clones with inserts of 80 to 150 kilobases (page 15, [0156]). Paragraph [0053] states:

"[0053] In one specific embodiment of the combined DNA and tissue arrays, the DNA array may be a cDNA or genomic microarray chip that allows a plurality (hundreds, thousands, or even more) of different nucleic acid sequences to be affixed to the surface of a support to form an array. Such a chip may, for instance carry an array of cDNA clones, oligonucleotides, or large-insert genomic P1, BAC, or PAC clones. These arrays enable the analysis of hundreds of genes or genomic fragments at once to determine their expression or copy number in a test specimen." (emphasis added)

Paragraphs [0152] and [0153] state:

"[0152] In Comparative Genomic Hybridization (CGH), DNA from a sample tissue, such as a tumor, is compared to normal human DNA. In a particular example of CGH performed by Vysis, Inc., this is accomplished by labeling the sample DNA with a fluorescent dye, and the reference ("normal") DNA with a fluorescent dye of a different color. Both DNAs are then mixed in equal amounts and hybridized to a DNA chip. The Vysis chip or genosensor, contains an array of large insert DNA clones, each comprising approximately 100,000 nucleotides of human DNA sequence. After hybridization, a multi-color imaging system determines the ratio of colors (for example green to red fluorescence) for each of the probe spots in the array. If there is no difference between the sample DNA and the normal DNA, then all spots should have an equal mixture of red and green fluorescence, resulting in a yellow color. A shift toward green or red for a given spot would indicate that either more green or more red labeled DNA was bound to the chip by that probe sequence. This color shift indicates a difference between the sample and the reference DNA for that particular region on the human genome, pointing either toward

amplification or deletion of a specific sequence or gene contained in the clones positioned in the array. Examples of genetic changes that can be detected include amplifications of genes in cancer, or characteristic deletions in genetic syndromes, such as Cri du chat.

[0153] Since each genetic region to be analyzed needs to be represented on the chip in only 1 or few replicate spots, the genosensor can be designed to scan the total human genome for large deletions or duplications in a single assay. For example, an array of just 3000 different clones evenly spaced along the human genome would provide a level of resolution that is at least 10 times better than what can be achieved with metaphase hybridization, at a much lower cost and in much less time. Specialty chips can be tailored to the analysis of certain cancers or disease syndromes, and can also provide physicians with much more information on routine clinical analysis than currently can be obtained even by the most sophisticated research laboratories." (emphasis added).

Finally, paragraph [0156] states:

"[0156] In one particular embodiment of CGH, a DNA chip or genosensor (hence, genosensor CGH or gCGH), such as an AmpliOnc.TM. chip from Vysis, contains an array of P1, BAC, or PAC clones, each with an insert of human genomic DNA. The size of these inserts ranges from 80 to 150 kilobases, and they are spaced along the human genome to improve the resolution of this technique. Since the hybridization probe mixture contains only on the order of 200 ng of total human DNA from each of the test and reference tissue, the total number of available probes for each arrayed target clone is relatively low, placing higher demands on the sensitivity of this system than what is needed for regular fluorescent in situ hybridization techniques. These demands have been met with the development of improved chip surfaces, attachment chemistry, and imaging systems. The combination of such features can provide a

sensitivity of $<10^8$ fluorophors/cm^2, which is achieved through highly efficient background reduction." (emphasis added).

Therefore, contrary to Appellant's assertions, in these four paragraphs Kallioniemi et al. specifically teach arrays which are ordered arrangements of spots with known locations, as the hybridization intensity is determined at each spot (see, for example, the description in paragraph [0152]), in view of Kallioniemi's definition of an array (paragraph [0022]):

"[0022] A "nucleic acid array" refers to an arrangement of nucleic acid (such as DNA or RNA) in assigned locations on a matrix, such as that found in cDNA or CGH arrays."

B) Fig. 14 does not demonstrate that Kallioniemi teaches an array of clones at known locations, according to their description of the Figure in paragraph [0048].

However, here is the description of the results represented in Fig. 14 (paragraph [0160]):

"[0160] This Example demonstrates how target genes for chromosomal gains seen by comparative genomic hybridization (CGH) can be rapidly identified and studied for their clinical relevance using a combination of novel, high-throughput microarray strategies. CGH to metaphase spreads (FIG. 14, chromosomal CGH) showed high-level DNA amplifications at chromosomal regions 7q31, 8p11-p12 and 10q25 in the Sum-52 breast cancer cell line. Genomic DNA from the Sum-52 cell line was then hybridized to a novel CGH microarray (FIG. 14, genosensor CGH, Vysis, Downers Grove, Ill.), which enabled simultaneous screening of copy number at 31 loci containing known or suspected oncogenes (the loci are shown in FIG. 13). This gCGH analysis implicated specific, high-level amplifications of the MET (at 7q31) and FGFR2 (at 10q25) genes, as well as low level amplification of the FGFR1 gene (at 8p11-p12), indicating the involvement of these three genes in the amplicons seen by conventional CGH analysis." (emphasis added).

Therefore, this paragraph and Fig. 14 provide additional description of an array used to determine gene amplification, i.e., increased number of gene copies.

C) There is no disclosure, teaching or suggestion of Kallioniemi of the "observing" step of claim 1, since Kallioniemi fails to disclose, teach or suggest an amount and location of labeled genomic nucleic acid hybridized to each immobilized probe, to detect regions of amplification or deletion in the sample, wherein positional information of clones on the arrays and chromosomes is correlated, thereby generating molecular profile of the chromosome or genome of the sample.

Paragraphs [0013], [0016] and the above-cited paragraph [0160] specifically teach determination of the amount and location of the labeled probe, and, since the array has an ordered array of clones corresponding to known regions of the chromosome(s), this information directly and inherently correlates location of the probe to the position on the chromosome. Paragraph [0160] was cited above, paragraphs [0013] and [0016] are cited below:

"[0013] In this method, the gCGH array can be assayed for a gene amplification, or a genetic or molecular marker that reflects this amplification. The CGH array can be a microarray that contains target loci that undergo amplification in cancer.

[0016] In another aspect, the invention features a method for detecting a genomic target sequence that is associated with a specific genetic disorder by contacting a plurality of genomic regions in a genosensor comparative genomic hybridization (gCGH) array with a nucleic acid test sample including nucleic acid fragments that collectively represent DNA from a cell with a known specific genetic disorder under conditions that allow the nucleic acid fragments to hybridize to one or more candidate genomic regions; measuring the amount of nucleic acid test sample hybridized to the candidate genomic regions, if any, and selecting a candidate genomic region corresponding to an altered amount of hybridized test sample nucleic acid compared to a

control sample of normal DNA; preparing a nucleic acid probe that hybridizes to the selected candidate genomic region; contacting a plurality of tissue samples with the probe under conditions that allow the probe to hybridize to nucleotide sequences in the tissue samples; and selecting a candidate genomic region corresponding to a probe that hybridizes to a significant number of tissue samples as a genomic target sequence that is associated with the specific genetic disorder."

Therefore, again, contrary to Appellant's assertions, Kallioniemi et al. specifically teach the observation step.

In conclusion, Kallioniemi et al. specifically teach all of the limitations of claim 1 except the limitation that the targets which are contacted with the arrays are shorter than 200 bp.

D) Proceeding now to the McGill et al. reference, Appellant states the following: "With reference to claim 1, McGill does not disclose, teach or suggest the particular size of the labeled, genomic nucleic acid fragments recited in claim 1." Appellant further argues that McGill et al. do not teach nucleic acid fragments in the range of recited in claim 1. Appellant has provided a table in which the probes of McGill et al. are equated with the array probes of Kallioniemi et al., not with the nucleic acid fragments used for hybridization to the probes. This most likely results from Appellant's confusion over the function of the probes of McGill et al., which are equivalent to the nucleic acid target fragments of Kallioniemi et al. being hybridized to the probes.

McGill et al. specifically teaches detection of chromosomal amplifications by hybridizing short probes with lengths between 10 and 500 bp, with the optimal probe sequence being 20 bp long (= nucleic acid fragments of targets in the notation of Appellant's claim language) (col. 3,

lines 56-67; col. 4, line 16; col. 5, lines 35-45 and 52-55; col. 6, lines 1-10) to the chromosomes (= probes in Appellant's language).

Therefore, McGill et al. specifically teach hybridization of chromosomes, i.e., very large DNA "probes", with short, 10-500 base pairs probes, i.e."targets".

E) As to the motivation to combine the references, Appellant states the following: "In addition, no objective evidence has been provided that the person of ordinary skill in the art would be motivated to combine Kallioniemi with the prostate cancer diagnosis methods of McGill. Appellant further argues that neither the Abstract of Pollack nor page 46, first paragraph of Pollack discloses, teaches or suggest the particular labeled fragment size recited in claim 1, i.e., less than about 200 bases.

The motivation to combine the references (i.e. the evidence) has been provided and is recited again here:

"Therefore, since the probes of McGill et al. are shorter than 200 bp, the result of using them in hybridization would be less probe aggregation and lower hybridization background, since each of the probes would anneal to a 20 bp sequence which appears once in 4^{20} bp in the genome, or once every 1,099,511,627,776 bp in the genome (as compared to human genome size of 3,000,000,000 bp), that binding of such probes will be very specific, therefore reducing background and non-specific aggregation.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used short probes of McGill et al. in the hybridization method of Kallioniemi et al. The motivation to do so, provided by McGill et al., would have been that probes with about 20 bases allows formation of duplexes which are stable and selective (col. 6, lines 1-3). Additional motivation for using short probes is provided by Pollack et al., who teach

hybridization of DpnII digested and labeled genomic DNAs to cDNA arrays (Abstract; page 46, first paragraph). They found that reducing the size of genomic DNA before labeling improved labeling efficiency by providing greater accessibility of the DNA template following digestion. Such greater accessibility would also allow more specific annealing of the probes to the array."

The fragments generated by Pollack et al. (page 46, first paragraph) were obtained by a digest with DpnII. As one of ordinary skill knows (or would be able to find out), DpnII has a recognition site of 4 bp, therefore, it will cut on average every 256 bp in a target DNA. In reality, the range of fragments obtained would be between 200-500 bp, depending on the length of digestion. Therefore, Pollack et al., who already started with relatively short fragments, recommended making them even shorter for increased labeling efficiency. Therefore, while McGill et al. provide motivation to use short probes for increased specificity and selectivity of hybridization detection, Pollack et al. provides motivation to decrease the probe size to increase the efficiency of probe labeling, which, again, would increase hybridization sensitivity and specificity.

F) With regards to the Mackey et al. and Gibco BRL Catalog, the latter was used as evidence to the reference of Pollack et al. to show that Pollack et al. specifically teach labeling of both strands of genomic DNA. As to the Mackey et al. reference, it provides a motivation for labeling both strands of DNA, not a motivation to use short probes.

In conclusion, claims 1-6, 12-14, 17, 67, 68 and 72 are unpatentable under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al.

III. Rejection of claims 7, 8 and 10 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., in view of Anderson.

Appellant argues that Kallioniemi either alone or in combination with any other references does not render claims 7, 8 or 10 obvious for the reasons already stated, and, since "the motivation to combine teachings of the cited references must exist in the cited references themselves, it is improper to use Anderson as the motivation to combine Kallioniemi, McGill, Pollack and Mackey. Appellant cited MPEP 2143.01 in support.

Appellant further states that no proper combination of cited references was provided to render claims 7, 8 and 10 obvious. Finally, Appellant states that even if the motivation to combine the references exists, Anderson does not cure the deficiencies of Kallioniemi, McGill, Pollack, GibcoBRL or Mackey, since Anderson does not disclose fragmentation of target genomic DNA that has both strands labeled with a detectable moiety, and Anderson shows only an agarose gel of DNA digest of lambda DNA.

Regarding the combination of Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., the arguments were presented above. Further, Anderson is not being used to provide the motivation to combine these references, but for the teaching and motivation to use enzymatically digested DNA fragments. Further, Appellant is quite mistaken as to where the motivation to combine the references comes from. In fact, the first three paragraphs of MPEP 2143.01 state the following:

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to

combine references. Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so >. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) (discussing rationale underlying the motivation-suggestion-teaching requirement as a guard against using hindsight in an obviousness analysis). The teaching, suggestion, or motivation must be< found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also In re Lee, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992)." (emphasis added).

Finally, as explained in the rejection, Kallioniemi et al. already specifically teach labeling of nucleic acids by polymerase chain reaction, nick translation or random priming. Anderson is

used to provide teaching and motivation for enzymatic fragmentation of nucleic acids. Therefore, the motivation in this case is contained in the reference.

Therefore, claims 7, 8 and 10 under 35 U.S.C. 103(a) are unpatentable over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., in view of Anderson.

IV. Rejection of claim 9 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., in view of Anderson, and further in view of Waggoner et al.

Appellant argues that Kallioniemi either alone or in combination with any other references does not render claim 9 obvious for the reasons already stated, and, since "the motivation to combine teachings of the cited references must exist in the cited references themselves, it is improper to use Anderson as the motivation to combine Kallioniemi, McGill, Pollack and Mackey. Appellant cited MPEP 2143.01 in support.

Appellant further states that no proper combination of cited references was provided to render claim 9 obvious. Finally, Appellant states that even if the motivation to combine the references exists, Waggoner does not cure the deficiencies of Kallioniemi, McGill, Pollack, GibcoBRL or Mackey, since Waggoner does not disclose fragmentation of target genomic DNA that has both strands labeled with a detectable moiety. Therefore, the disclosure of Cy3 and Cy5 of Waggoner does not render claim 9 obvious.

Regarding the combination of Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., the arguments were presented above. Further, Anderson is not being used to provide the motivation to combine these references, but

for the teaching and motivation to use enzymatically digested DNA fragments. The argument regarding the motivation to combine references was addressed above.

Finally, as explained in the rejection, Kallioniemi et al. already specifically teach labeling of nucleic acids by polymerase chain reaction, nick translation or random priming. Anderson is used to provide teaching and motivation for enzymatic fragmentation of nucleic acids, whereas Waggoner et al. provide specific teaching and motivation to use Cy3 and Cy5 as fluorescent labels.

Therefore, claim 9 under 35 U.S.C. 103(a) is unpatentable over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., in view of Anderson and further in view of Waggoner et al.

V. Rejection of claim 11 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., in view of Anderson, and further in view of Ordahl et al. and Anderson.

Appellant argues that Kallioniemi either alone or in combination with any other references does not render claim 11 obvious for the reasons already stated. Appellant further states that Ordahl discloses a technique that produces DNA fragments of approximately 230 base pairs, whereas claim 11 requires fragments smaller than about 200 base pairs by shearing followed by enzymatic digestion. Anderson does not disclose fragmentation of target genomic DNA that has both strands labeled with a detectable moiety, and Anderson shows only an agarose gel of DNA digest of lambda DNA, therefore no evidence has been provided that the combination of cited references discloses all elements of claim 11.

Regarding the combination of Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., the arguments were presented above.

As explained in the rejection, Kallioniemi et al. already specifically teach labeling of nucleic acids by polymerase chain reaction, nick translation or random priming. Anderson is used to provide teaching and motivation for enzymatic fragmentation of nucleic acids, whereas Ordahl et al. provide specific teaching and motivation to use shearing forces to fragment DNA. The fragments created by Ordahl et al. have an average size of 230 bp, which means that there are fragments shorter than 230 bp, but Anderson is used here to provide teaching and motivation to digest the fragments to below 200 bp.

Therefore, claim 11 under 35 U.S.C. 103(a) is unpatentable over Kallioniemi et al., McGill et al. and Pollack et al., as evidenced by Gibco BRL Catalog and Mackey et al., in view of Anderson and further in view of Ordahl et al. and Anderson.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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